

Lente (F. D.)

ON THE

TREATMENT OF INTERMITTENT FEVER

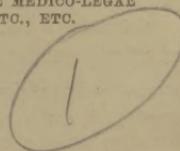
BY THE

HYPODERMIC INJECTION OF QUININE.

BY

FREDERIC D. LENTE, M. D.,

MEMBER OF THE BOARD OF MANAGERS OF THE HUDSON RIVER STATE HOSPITAL; OF THE MEDICAL SOCIETY OF THE COUNTY OF NEW YORK; OF THE MEDICAL SOCIETY OF DUTCHESS COUNTY, N. Y.; OF THE PATHOLOGICAL SOCIETY OF NEW YORK; HONORARY MEMBER OF THE MEDICAL SOCIETY OF NORTH CAROLINA; CORRESPONDING MEMBER OF THE MEDICO-LEGAL SOCIETY OF NEW YORK, ETC., ETC.



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JOHN BROWN

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1900-1901. (See also the following page for 1901-1902)

## ON THE TREATMENT OF INTERMITTENT FEVER BY THE HYPODERMIC INJECTION OF QUININE.<sup>1</sup>

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THE author of an able review of works on hypodermic medication, in the *American Journal of Medical Science*, remarks: "In the treatment of malarious fever, hypodermic medication bids fair to yield as brilliant and substantial results as for any other disease. There certainly need be no great delay in deciding its merits, and fixing any detail of treatment. As in many sections of our country malarious fevers are the prevailing diseases during a considerable portion of the year, there is abundant opportunity for trial, as there will be an overflowing measure of benefit resulting, should the observations already published be substantiated." He adds: "We think it would be difficult to exaggerate the importance of this improvement in our art to those portions of our country scourged by malaria, and we cannot refrain from again urging an investigation of its merits upon the profession, requiring as it does no complicated apparatus, no trained skill in delicate manipulation, but simply a spirit of enterprise, careful observation, and candid report of results."

Being fully in accord with the sentiments above expressed, I have, for the past two years, been endeavoring to surmount some of the difficulties attending the practical application of this method of treatment, and to test the value of the reports heretofore published; and now present the results of my un-

<sup>1</sup> Read before the Dutchess County Medical Society, January 14, 1874.

finished labor in this direction, merely as a contribution to the work, being fully alive to the fact that my experiments, though more extensive than any yet published, are not sufficiently so to *settle* the question as to its relative value, or the details of its execution.

It appears that Dr. Chassaud, of Smyrna, was the first experimenter with the hypodermic use of quinine. This was probably in 1861 or 1862; yet, after the lapse of eleven or twelve years, we have only occasional and meagre reports of its employment, and evidently very little faith among the profession in its safety or efficiency. This has arisen probably from at least two causes: one, the rose-colored hue of the early reports;<sup>1</sup> but principally the unpleasant accidents which have generally followed the injection of the solutions usually employed by physicians during the past few years. It has been my aim, therefore, to properly estimate the true value of the method in intermittents, and to overcome, by extensive trial, the pharmaceutical obstruction to its more general adoption.

Dr. Chassaud reports that, "of one hundred and fifty cases, he saw but one relapse after three months, using generally but a single injection." "Goudas reported fifteen cases, with like result. Eulenberg reports two cases of arrest of the cold stage by two grains; and reports two cases in which a single injection in the apyrexia checked the disease permanently." "We have, in two instances," says the reporter (*American Journal of Medical Science*) above referred to, "injected that amount of quinine an hour before the chill, and put a stop to the disease." Dr. James McCraith, surgeon to the Smyrna and Aiden Railroad, reported to the Royal Medical and Surgical Society, that he had found it very useful in the "pernicious intermittents," and gave one case of an alarming character, where three and a half grains produced a rapid rescue from coma and impending death. Dr. Moore, of the Bombay

<sup>1</sup> The fact that the cases reported were mostly in hospital practice will account for the great apparent success, perhaps; as an hypodermic injection of even four or five grains will generally check the disease for two or three weeks, and as patients are not apt to be kept in hospital long after the symptoms of disease disappear, the cases would be marked cured.

Hospital, reports its 'use in thirty cases of intermittent, and some cases of remittent, with "almost invariable success." In intermittents, he states that one injection sufficed, while, in remittents, he employs five or six. Dr. Greene, of Americus, Ga., in an article on this subject in the *Louisville Medical Journal*, 1871, speaks highly of the hypodermic use of quinine, but has seen "such serious inflammation and sloughing follow its use" as to cause him to discard it except in dangerous "congestive chills." But he expresses the hope that some preparation of the drug may be devised which will render it more generally applicable. The reason of his ill success is evident from the composition of his formula. The late Dr. H. D. Bulkley tried this plan in the New York Hospital, in some cases, and reported them at a meeting of the New York Academy of Medicine in 1866. He stated that he had the most gratifying results, "especially in pernicious intermittents from the South." His colleague, my friend Gouverneur M. Smith, M. D., according to Dr. Bulkley's report, also used this method in the same hospital, "with most gratifying results." Dr. Otto's experience will be noticed farther on. I have been told, by some of the resident medical officers of the Bellevue Hospital, New York, of some trials of this method there, but have never been able to get any details; and they did not seem to be *impressed* with its success, especially in pernicious fever, in which it was almost exclusively used. But the cases were, as I understand, of a rather desperate character. It would appear that, up to the present time, almost all the published experiments with this method have been carried on in public institutions; and there seems to be a general impression that it will admit of a very limited introduction into private practice. The experience of the writer will show that this is not correct. With patients who are kept in a proper state of discipline, and by judicious management, nine-tenths will submit to one injection at least; and, among those who are victims to repeated attacks of fever, who have exhausted a variety of remedies, and their own patience also, who are suffering from the demoralizing influence of malarial toxæmia, with no "let-up" to its painful symptoms, there will be no hesitation when the treatment is proposed,

with a proper explanation of its *modus operandi*, even though they or their acquaintances may have suffered from local troubles resulting from it. I have injected many patients this year who suffered from troublesome inflammation and abscess last year.

Let us first consider the *accidents* which are alleged to have occurred and to be liable to occur from this treatment. Inflammation of a circumscribed character, abscess, and sloughing, have frequently followed this procedure, and to such an extent as to have deterred most physicians from resorting to it, although many have been anxious to do so. Even *tetanus* has been charged to it. Notwithstanding the very favorable reports from tropical regions referred to, Dr. Maclean, of Netley Hospital, reports that, "of four cases in the hospital who had been thus treated, three had troublesome ulceration." Of the last one hundred cases reported in the *Indian Medical Gazette*, sixteen are said to have suffered from "ulcerations." The nature of these is not described. Sixty-eight of the cases are reported "cured." I have heard and read of cases where sloughing occurred, laying bare the muscles, etc.; and I have had two slight sphacelations in my own practice, one quite tedious, the other a regular "dry gangrene," attended, from first to last, by perfect anaesthesia of the part; an incision giving rise to a hard, sloughy mass (on the thigh) with a rapid and painless healing of the wound; the patient caring little about it, and ready at any time to submit to the operation again, which he had already submitted to several times with perfect impunity. Last year, when I was a novice in the method, and experimenting with solutions of various composition, I had many cases of inflammation and abscess, some of them exceedingly protracted and very annoying. Indeed, the inflammatory process, set up by solutions of quinine, and often by morphine also, and by other fluids, is peculiar. In many cases, days and even weeks may elapse before any marked trouble occurs, when a slow form of inflammation is set up, which results in a chronic abscess very little disposed to discharge spontaneously. In other cases, a tender induration merely remains for weeks or months, not causing any serious annoyance, and the soreness sometimes subsiding for days, to

reappear again and again. The same solution, injected into a dozen patients, and perhaps in some of them in several places, may be perfectly harmless in a majority, but give rise to very troublesome *sequelæ* in a certain number; the general condition of the subjects being the same, or very likely of a more unfavorable character in those escaping the inflammatory trouble. I have said that tetanus has been charged to hypodermic injection of quinine; and, as the slightest probability of this would be an insuperable obstacle to the employment of this method, the allegation is worthy of notice. Two cases are reported in the *Indian Medical Gazette* of 1873 by a Dr. Odevaine, in which he injected a solution of quinine, which was followed by abscess and fatal tetanus. M. Arnold, of Algeria, also reported two cases of the same kind a few years since. I have heard of no such occurrences in this country, and it is well to remember that there are certain localities, mostly tropical, where tetanus occurs as a very common incident from the most trivial wounds; and even idiopathically, from exposure to damp, or sudden check of perspiration. I have elsewhere discussed this subject.<sup>1</sup> It is needless to say that it is the *wound and abscess* in those cases, and not the quinine-injection, which caused the disease. Still, *in such localities*, no prudent physician would subject his patient to such a risk.

A properly-prepared *solution of quinine* is, of course, the important desideratum, and several were proposed to me, as having given satisfaction, but which were found to be impracticable. As an example of the extraordinary mixtures which have been highly recommended for hypodermic injection, I quote from the (London) *Practitioner*, for September, 1872, one by Dr. Otto, given in *Le Mouvement Médical*: "The quinine," he says, "should be dissolved in ether, which should then be filtered and allowed to evaporate to some extent, so that more concentrated solution may be obtained." Now, quinine is so nearly insoluble in ether that, for all practical purposes, it may be so considered. Prof. Maclean, of Netley Hospital, recommends an equally impracticable solution. In his report on the hypodermic injection of quinine, which was pub-

<sup>1</sup> Article on "Jamaica," in *NEW YORK MEDICAL JOURNAL*, September, 1868.

lished officially in India, he says: "It is quite possible, with a little care, to inject six grains of the salt (sulphate of quinine) in twelve minims of water, without the aid of any acid. The proceeding is very simple. Three or six grains are placed in a watch-glass, previously warmed; to this, twelve minims of distilled water are added, and a moderate degree of heat applied, with a spirit-lamp, for a second or two." Then he proceeds to give minute directions, as to the warming of the syringe, the size of the trocar, etc., which I do not transcribe, as I doubt if any one will be able to get the solution ready. The mass will be found to be a semi-fluid paste before heating, and less fluid after. If we could, in this way, get six grains in *sixty drops* of water, it would be superior to any solution which I have heard of, or been able to produce by long experiment. Dr. Moore says: "I have used the strongest solution which can be prepared, viz., thirty grains quinine, eight or ten drops of dilute sulphuric acid, and half an ounce of water." Dr. Lorent uses acetate of quinine, of which he says, "thirty grains will dissolve, by the aid of heat, in two and a half drachms of water." Dr. Greene's solution, which gave him so much trouble, is: "R. Quin. sulph. 3ss; acid. sulph. dil. gtt. x; aquæ bul. 3ss M." The formula employed in the New York Hospital is: "R. Quin. disulph. 3j; acid. sulph. dil. gtt. 1; aquæ font. 3j. Solve." Dr. Constantine Paul highly recommends glycerine as a solvent. The last suggestion has a great advantage over the others, in promoting the solubility of the drug with very little acid, and retaining it in perfect solution. But, unfortunately, it is irritating to the cellular tissue, very slow of absorption by it, and very prone to flow away from the small puncture after its injection. After failing with all the solutions hitherto recommended, I applied to a practical chemist, in New York, to prepare for me a solution which should contain "ten grains of the salt to the drachm, with the least possible amount of acid which will retain it in solution." His solution, as he stated, contained a minim of strong, or fourteen minims of diluted, sulphuric acid to the drachm. Notwithstanding this amount of acid (about four times the amount used by Dr. Moore, six times that of Dr. Greene, and about seventy per cent. more than the New York Hospital formula),

his solution was not permanent, but deposited crystals abundantly, unless kept at a temperature of 70° or 75° Fahr. It was, therefore, generally necessary, in cool weather, to heat it before using. How previous writers have managed, therefore, to prevent their solutions from depositing, or to use them without the aid of heat, is a mystery to me. As regards Dr. Lorent's solution, I have not tried it, for I had so uniformly failed with formulæ for dissolving the different salts of quinine without acid, so confidently recommended, that I had no greater faith in the solubility of the acetate than of the bromide, the bisulphate, the hydrochlorate, etc. Before using the ten-grain solution, I had tried a much weaker one, only four grains to the drachm. But, as the injection of even pure water into the areolar tissue is quite irritating, it was a nuisance, both to the patient and physician, to be obliged to inject a drachm of fluid in order to introduce so small a quantity of the drug into the system. After using the stronger solution for some weeks, and finding that I was getting a rather inconvenient crop of inflammation, abscesses, and sloughs, and creating a damaging but very natural prejudice against a very valuable remedial measure, I reduced the strength to five grains to the drachm; but the smallness of the dose and the still frequent occurrence of inflammation and tumefaction induced a trial of some further modification. I had also been annoyed by a cryptogamic deposit in the solution after standing for a short time; and, with a view to obviate this, and also to test the efficacy of Lister's antiseptic plan on the cellular tissue, carbolic acid was added to the solution; and, after some trials, the following formula was adopted, and has been used ever since: Rx. Quinae disulph. gr. 1; acid. sulphuric. dilut.  $\pi$ c.e.; aquae font.  $\xi$ j; acid. carbolic., liq.,  $\pi$ v. Solve. Place the quinine and water in a porcelain dish, over a spirit-lamp, heat to the boiling-point, and add the sulphuric acid, stirring with a wooden spatula. Filter at once into a bottle and add the carbolic acid. This gives full six grains to the drachm. Even this solution will deposit some crystals at a temperature of 50°; and, of course, at or below that temperature requires to be warmed before using. The carbolic acid also, I think, alleviates the pain of the injection, as there

is but little complaint, in most cases, after the first few drops. I can recommend this with considerable confidence, so far as danger of local difficulty is concerned, since it has been used by myself and my various assistants at least one hundred and fifty times, or over three hundred insertions (each hypodermic *dose* consisting of at least two injections). Neither have I, nor any of the gentlemen who have used it under my direction, had any serious trouble with it.<sup>1</sup> In one case, after using it twice, it produced each time a diffuse cellular inflammation of the arm, which yielded slowly to cold-water applications, and I desisted, although the patient was anxious to submit to another trial, so far superior did she find this method to that by the mouth. In another exceptional case, a singular effect was produced, already noticed in this paper—anaesthesia of the part, followed by dry gangrene of a small mass of cellular tissue. This was the fourth injection of this patient, or the eighth insertion, none of the others giving any trouble whatever. Patients frequently experience a numbness of the part, sometimes lasting weeks after the operation, possibly from the effect of the carbolic acid. The injected part is usually tender for a few days after injection, when accidentally touched; sometimes inconveniently so, when the patient is at manual labor (on this account, it is better to select the left arm), but it rarely incapacitates a laborer, even for half a day. Since this solution has been used, I have met with full as many cases of trouble arising from injections of *morphine*, though so much smaller in bulk, as from it. All hypodermic injections, however small, will occasionally cause inflammation, abscess, and even sloughing, sometimes of a persistent character.

The question of the proper strength and composition of the solution is a vital one, as regards the ultimate success of this valuable mode of treatment, and, as it cannot be considered at all settled, I have already dilated considerably on this point, and would remark further that the inconvenience, slight

<sup>1</sup> Dr. Murdock has used this method to a moderate extent, and his experience is incorporated with mine. I have, at different times, been assisted by Dr. A. A. Smith, of New York, and by Drs. Farmington, Griffith, and Young, of the resident staff of Bellevue Hospital, who are, I understand, using this solution now in that hospital.

though it is in a majority of cases, of introducing the needle two and occasionally three times at a sitting, and inserting sixty to ninety minims of fluid more or less irritating, is sufficient to induce the hope that a solution equally safe will be devised, which shall contain two or three times as much of the drug. It is true that, by the aid of heat, *applied at the time of the injection*, double the quantity in the same amount of fluid may be used ; and this brings up the question of *concentration* of the solution, which most writers have considered essential. Two ideas seem prominently to occupy the minds of those who have employed this method, both of which are probably erroneous and mischievous : one, that the solution cannot be too concentrated, provided little or no acid be used ; the other, that the acid is the principal or only cause of the serious accidents sometimes attending the injections. Now, it will be found that, in cases of local trouble, more than one cause is in operation, sometimes several. Thus the delay in the absorption of the fluid, one portion of areolar tissue only a few inches from another absorbing more readily ; this delay being also sometimes attributable to the *imperfect solution of the salt*, and the latter the result usually of using *too little acid*. The character and condition also of the *instrument* is perhaps a not infrequent cause. The manner of performing the operation, slight as it is, has its influence. Dr. Moore says, "I insist on a perfectly clear solution of the alkaloid," and he might have added, at a *temperature of 60 Fahr.* I am inclined to think that the *acid*, so largely diluted as it is, even in the solution advocated here, 1.7 per cent. of the undiluted, can have no injurious effect on the tissues greater than that of the other agents employed, if as great, and that there is more danger in using too little than too much. The longer the solution remains in contact with the areolar tissue, the greater the danger of inflammation ; and the more *complete* the solution, the more rapid, *ceteris paribus*, the absorption. Here is a very recent case in illustration of this fact : A young girl was injected five days ago, with two syringefuls of solution. One passed readily into the circulation ; the other remained, and was disposed to exude through the puncture ; the finger was kept on for some time to pre-

vent it ; but the fluid passed away for some hours, drop by drop. The parts about this puncture are much inflamed, and, notwithstanding the application of cold, there is still some redness and induration, while the other puncture has given no trouble at all.

Having settled upon a proper solution as far as present experience enables us, there are some precautions advisable. It is important to have a *gold* needle, not one merely gilded. Messrs. Tiemann & Co. prepare them very skillfully, and, with care, they seldom require sharpening, which may easily be done on a fine hone. The syringe and needle should be washed out after each operation, and the piston frequently oiled, as it is both stiffened and rotted by the solution. The outer and anterior portion of the *arm*, not too near the joints, are usually chosen for the insertions, although the outer and upper portion of the thigh present desirable localities. We have, however, injected all parts of the body, in cases where repeated injections were required. I usually make the two punctures two and a half to three inches apart, so that the wet application, which is often desirable, to prevent inflammation, may cover both. The injection should be made with deliberation. The first few drops cause more or less severe smarting, and I wait until this ceases, or nearly ceases, perhaps half a minute or a minute ; then continue *slowly*, drop by drop, as fast as the patient can endure it, without inconvenient pain, being guided also somewhat by the rapidity with which absorption takes place, judging by the greater or less elevation of the integument around the puncture. As soon as the needle is withdrawn, I cause the patient or a by-stander to put the finger over the puncture for two or three minutes, to prevent the fluid from exuding. In case of threatened inflammation, or much soreness, I direct the patient to bind on a wet folded handkerchief or pledge of lint as a precautionary measure.

As regards the best *time* for the operation, the general impression seems to be that it should be done just previous to the expected paroxysm, and Dr. Moore, of Bombay, says : " The best time is shortly before the cold fit ; but it may be done during the cold stage with the effect of lessening and sometimes stopping the whole paroxysm." I can corroborate the

last observation, and shall subjoin some cases in illustration of this important point.<sup>1</sup> I am not fully prepared, as yet, to say whether there may *not* be an advantage *as regards the ultimate effect of the operation*, in following the prevalent notion. But, it so often happens that the severe train of symptoms attending a paroxysm of *epidemic* ague is mitigated, even arrested by the injection on the spot, that, when convenient, I always give the patient the chance. But, as a general rule, I have injected without any reference to the date of the paroxysm. This point will bear further investigation. I am informed, however, by Dr. Meredith Clymer, that, in a recent report of English army-surgeons serving in malarious regions, the verdict is decidedly in favor of administering quinine (this does not refer to the hypodermic method) *during* the attack.

As regards the *dose*, it depends, like that administered by mouth or rectum, on so many circumstances that one cannot be definite. But the *variation*, depending on *idiosyncrasy* and age especially, is not nearly so great as in the other methods. The doses of various reporters have varied from two to ten grains. The fact is that, at present, it is limited somewhat in obstinate cases by the insolubility of the drug, a dose of twelve or eighteen grains requiring of the solution here recommended two or three drachms, too large an amount of fluid except in desperate cases, where severe pain and abscesses are comparatively of little moment. My first doses were two or three grains, and the most marked results were obtained from these small doses, probably because the medicine was more largely diluted, the same quantity of fluid being always used; possibly also because the disease assumed a more obstinate type as the epidemic wore on. For the latter reason it was found necessary to increase the dose to *six grains*, and in a few cases to nine or ten grains. When more than six grains were employed, I usually made three injections, but

<sup>1</sup> I have long been in the habit of injecting *morphine* gr.  $\frac{1}{2}$  in the paroxysm of intermittent fevers, preferably in the cold stage, to the infinite relief of the patient, and the arrest of the paroxysm to a considerable extent. When the suffering is particularly severe, it is better to combine the morphine and quinine. I described this method in a letter to the late Prof. Elliot, published in the NEW YORK MEDICAL JOURNAL in 1870.

sometimes used a syringe of greater capacity, and only inserted twice. When the patient has a good deal of adipose tissue, and is not particularly intolerant of the injections, forty minimis may be used in one spot.

*Repetition of Doses.*—During a severe epidemic, it will usually be necessary to repeat the dose every fourteen or twenty days; in some cases every six days; and now and then every day or two. In these cases the patients are so tolerant of the injections that they care very little for them. Where the resulting soreness or inflammation is troublesome or tedious, it is better to resort, if possible, to some other treatment. During the intervals it will not usually be necessary to give any anti-periodic or tonic. In my own cases, desiring to test the value of the treatment as accurately as possible, I rarely gave any medicine, even of a cathartic nature, unless required by constipation.

Want of time, and the fact that cases under my charge would often, of necessity, pass into the hands of one of my assistants, and *vice versa*, and that cases of an obstinate character would sometimes be taken in hand by friends or nostrum-venders, and thus disappear, caused more or less confusion in my records, and have precluded as thorough and systematic investigation of the subject as I at first proposed. But, such as they are, I present my statistics to the profession, without waiting to attempt the solution of the various important questions involved, hoping that they may at least arouse more interest in the subject than my predecessors have done.

My own operations number 238 on 134 patients, or 476 insertions. Those of the other physicians, who have aided me in carrying out this treatment, number 151 on 63 patients, or 302 insertions; giving a total of 389 injections, or 778 insertions. These do not constitute all the injections of quinine which have been used by us during the past two years, but only such as have been recorded. In various ways failure to note injections occurred frequently, and Dr. Murdock did not commence regular notes of his cases until 1873. Of patients under eighteen years there were 29, the youngest five months; and it is remarkable that in no instance that I can call to mind has any unpleasant local or general result happened to

very young children—such as frequently occurred, especially during the first year, with adults, and with a similar solution. A few of the very young infants were injected a number of times, as vomiting was almost incessant.

In 104 cases only one injection (two insertions) was used; in 47 cases two operations; in 12 there were three; in 3 there were four; in 6 there were five; in 1 six; in 1 nine; in 1 ten; in 1 twenty; in 1 *twenty-nine*; in 1 *forty*.

In 9 cases it was noted that the hypodermic method succeeded after failure of quinine and other remedies by the mouth; in 17 cases, on the other hand, that no marked effect was produced by the injection. In 4 of these cases, however, less than five grains of quinine was injected, and a repetition of the operation might have led to a different result, many cases requiring large and repeated doses of quinine and other remedies, and a resort to various plans of treatment as each, in turn, lost its effect. In 4 others of these cases failure resulted from mistaken diagnosis, the disease proving to be continued fever, over which the injections have no control. The injection thus proved to be an important means of diagnosis; the symptoms of the beginning of these irregular forms of intermittent fever being almost identical with those of typhoid fever.

In 14 cases, prompt relief of the urgent symptoms, that is within half an hour, was experienced. In 14 cases the injection failed to check the disease as long as one week, and in these cases no further trial of the plan was made. It must also be borne in mind that some of the *successful* cases may have used remedies by the mouth without our knowledge, though care was taken to prevent, as far as possible, this source of confusion in the experiments. In some of Dr. Murdock's cases he used quinine by the mouth in conjunction with his injections.

In 21 cases vomiting is noted as having been so obstinate as to have precluded the administration of medicine by the mouth in any form, and generally of nourishment also. In every case this symptom was promptly relieved by the injection. The temperature, during the paroxysm, varied from 102° to 107°—rarely as high, however, as 106°.

In making deductions from these statistics, it is necessary to take into account the fact that many of the cases, occurring during the epidemic which has prevailed so extensively throughout a large extent of our country for the past three years, have been remarkably rebellious to treatment; that is, the disease, though arrested with comparative ease for the time, has very generally *recurred* under *any* treatment;<sup>1</sup> many cases requiring very large and repeated doses of quinine, and frequently a recourse to a variety of drugs and plans of treatment, as each in turn lost its influence; also, that in some cases, in which at first sight the treatment might appear to have been a failure, and which is noted in the above analysis as such (that is, as unsuccessful in *arresting* the disease), the benefit derived from it, as auxiliary to other remedies, was nevertheless very important: the arrest of vomiting, of severe cephalalgia, and other pains, sometimes the marked improvement of appetite and strength. Cases in illustration of this are appended.

In two particulars, the effect of the drug administered hypodermically differs essentially from its use by the mouth, viz., in seldom inducing severe cerebral symptoms; and in *promptly* imparting a feeling of vigor and hopefulness seldom observed after the usual methods.

To recapitulate—this method would seem, in the light of our present experience, to be particularly applicable to those fatal cases of the disease called “pernicious” or “congestive fever,” in which no reaction or a very imperfect one takes place, and a patient dies as in the collapse of cholera, because neither the *stomach* nor the *rectum* will absorb medicine even if they could retain it and there were time for it to act: to cases where *vomiting* is persistent, or where intense pain or other distress is a prominent symptom: to *quotidiants*, where the paroxysm is so protracted as to afford little time for the action of remedies by mouth or rectum: to patients who can-

<sup>1</sup> In ordinary cases of intermittent fever, such as I have met with in this locality for the past twenty years—that is, previous to this remarkable epidemic, which has invaded regions heretofore considered proof against malaria—I have no doubt the success of the hypodermic treatment would have equaled if not exceeded that of the reporters already quoted.

not tolerate quinine on account of cerebral symptoms: to the cases of the poor, and of laboring-men where promptness in action and cheapness of material are important considerations. Indeed, in an economic view, especially in the case of armies, of hospitals, and eleemosynary institutions, its advantage is very manifest, particularly in regions where the doses by the mouth need to be enormous; and from all parts of the world, temperate climates as well as tropical, where malaria prevails at all, we have reports of the necessity of these extreme doses in certain cases of epidemics—the doses varying from a scruple and a drachm, several times a day, to three drachms.<sup>1</sup> I quote the following, in illustration of this, from a letter just received from Dr. J. C. Young, resident physician of Bellevue Hospital, giving the experience of Dr. A. W. Woodhull, surgeon to the Ninth New York Volunteers, during the last three years of our civil war:

"The greater part of his experience was gained in the swamps of North Carolina, at Newport News, and around the city of Norfolk. He met the maximum number of cases at the first-named place, where, in addition to the malarious influences so rife there, the troops were subjected to some privations, and were, for a portion of the time, partially submerged in water. He saw upward of two thousand cases a year, a tolerably fair proportion of which had a tendency to assume the pernicious type. He himself suffered from the congestive chills. The first he did not recognize, and obtained relief by emesis. The congestion was pulmonary, and his face and extremities became livid, almost black. The second was relieved by a drachm of quinine, taken in two doses at an interval of five minutes. In other cases, he used 200 grains, and in some few 240 grains (the maximum) within twenty-four hours. The largest dose was, however, one drachm.

<sup>1</sup> Socin, Professor of Surgery in Basle, states (*London Practic.*, December No., p. 424) that, in the severe septicemic-wound fevers, during the Franco-German War, he employed quinine in the daily quantity of 6.7 grammes (90 to 105 grs.). "Under this treatment he saw many unexpected recoveries." He states also that the cinchonism was moderated by a considerable quantity of wine which he gave at the same time. No physician in Europe is more trustworthy than this able man.

He usually gave half-drachm doses at intervals of an hour or two—repeated until marked cinchonism was produced. He reports but few deaths, even when the patient suffered from the congestive variety ; and, in the fatal cases, death usually ensued from the inability of the patient to retain the large amount of quinine necessary to produce cinchonism."

I have selected the following typical cases, very briefly reported, as likely to be of interest to the profession, and in illustration of the preceding remarks and statistics :

*Cases in which very Small Doses were successfully used.*

CASE I.—Robert McC., aged forty years ; general health good. Quotidian four days, coming on in afternoon, lasting until morning. His sufferings intense, especially the cephalalgia ; and his vomiting for some hours uncontrollable. Has taken repeated doses of chinoidine, but could retain very little. Injected in the thigh four grains in one drachm of fluid. Next day, July 11th, much better. Repeat.

July 25th.—Patient remained quite well until August 2d, when, after riding twenty-seven miles in a hot sun, and being much overcome by heat and fatigue, he had a recurrence. He continued to have attacks at intervals, broken up temporarily by various methods, the injections having caused a troublesome abscess.

CASE II.—P., aged fifteen years. Has had fever all spring and summer, broken repeatedly by quinine and chinoidine, but sometimes recurring even while taking the medicine.

August 10, 1872.—Injected half a drachm (2 grs.).

11th.—Feels pretty well, and is at his work. Repeat.

21st.—Has remained well. Fever subsequently recurred, as I heard.

CASE III.—Mrs. McC., aged sixty-three years. In bad health for twenty-five years. Has suffered, more or less, all summer from irregular intermittent. Has taken quinine and chinoidine, but she is more or less under the influence of malaria all the time. Injected to-day, August 12th, one drachm (2 grs.).

August 20th.—Continues quite free from any manifestations.

28th.—Has been in better health since injection than she had been for six months. Has no recurrence.

CASE IV.—Mrs. M. R., aged sixty years; a feeble woman, always complaining of some ailment, and subject to attacks of uterine and nephritic disease. Has been having repeated attacks of quotidian. Has now dysentery (probably malarious), and is vomiting incessantly; can retain no medicine and is much reduced. Temperature 105°. Injected one drachm (4 grs.).

August 20th.—Has been pretty well; no symptoms of fever. Has taken no medicine. Some deafness remains.

September 8th.—Continues well.

CASE V.—Mr. N., a stout, healthy farmer, aged thirty-six years. Has had several attacks of fever, and has broken it by quinine, chinoidine, and nostrums. But the present attack (quotidian) is attended by unusual symptoms—violent abdominal and erural cramps, vomiting incessantly, great debility, cephalalgia, etc. Gave him yesterday an anti-emetic mixture and chinoidine pills; but they were rejected. His temperature was 106°. Had his chill to-day two hours ago. Temperature now 105°. Injected quinine solution 3 j (3 grs.).

August 17th.—Second day. Has passed over the time for attack two hours. Temperature 100°, skin pleasant, pulse feeble. Injected two grains.

20th—No fever since last date. Injected two grains.

21st.—Feels “more like himself,” as he says; able to work a little. Subsequently had another moderate attack.

CASE VI.—N., aged fifteen years, a stout, healthy lad, previous to his attacks of malaria, which have reduced him very much, notwithstanding a systematic course of quinine and chinoidine. Injected to-day, August 19th, half a drachm of solution (2½ grs.).

August 21st.—Is still very weak in his limbs; no fever. Injected one drachm (4 grs.).

24th.—Feels “a great deal stronger,” and better than he has been for a month. Injected one drachm (4 grs.).

September 5th.—Well.

CASE VII.—Mrs. W. W., aged forty-five years; a thin and feeble-looking woman always, but almost reduced to a skele-

ton now by long-continued attacks of malarious fever (two years). Has never succeeded in breaking it up for more than eleven days. Comes from New Jersey. Quinine has such an unpleasant effect on her that her physician told her she "must never take it again." Injected quinine two grains. The immediate effect was "faintness," and, within fifteen minutes, dizziness and excessive weakness, which marked the effect of the drug by the mouth. She could not walk without assistance, and was laid on a sofa with the head low, and a stimulant given. She made one or two attempts to vomit, but the disposition soon passed off; her surface was cold and clammy. Pulse not materially affected. She left the place the next day, and I heard from her some months after, as having continued free from fever, and gaining constantly in strength.

CASE VIII.—Mrs. M. Has been living on the other side of the Hudson River, several miles below. Has had intermittent for two summers. Broke it up last summer by a nostrum, but failed this summer. Chill is now due in four hours (quotidian). She applies, not for this trouble, but for the removal of her tonsils. Performed this operation, and then injected four grains of quinine.

*September 26th.*—Patient writes that she has had no return of fever.

*October 7th.*—Had no return of fever until yesterday.

*Cases in which Immediate Relief of Distressing Symptoms was obtained.*

CASE I.—M. L., aged seven years. Has had mild attacks during almost the whole summer; easily broken up by quinine, in full doses. Has also taken the drug pretty regularly in prophylactic doses. But the attacks recur. Has one now (August 29th). Injected 12 minimis of strong solution, 2 grains.

*September 6th.*—Has continued well.

15th.—Continued well until to-day, and was attacked with headache, nausea, etc. Injected 4 grains. Was relieved in fifteen minutes; fell asleep, and awakened entirely free from symptoms.

CASE II.—E. D., aged twenty-three; a stout, healthy girl. First attack two days ago.

*August 29th.*—Has chill on her now. Temperature  $103\frac{1}{2}$ °.  
Inject 4 grains.

*30th.*—Quite well to-day.

*September 6th.*—Has continued well until this morning. Has a chill. Inject quinine, 12 grains. In a few hours, the paroxysm having been cut short, she was able to resume her work. Feels only a little weak.

**CASE III.**—Sarah G., aged eleven years.

*August 29th.*—Has had quotidian for four days. Has been taking chinoidine regularly. But it has had no effect. The attack to-day is earlier and more severe. She is now shaking violently, and has a racking headache. Inject 4 grains. Within five minutes, the shivering ceased, and very soon the headache almost ceased.

*30th.*—Feels bright and well to-day.

**CASE IV.**—Mrs. T., aged forty; a stout, healthy woman, called me on August 30th, while in a violent paroxysm of ague. Intense headache, pain and soreness in abdomen and dorsal region of spine, also vomiting; has been suffering, more or less, for twelve hours. Has scarcely had any sleep for a week. Inject quinine,  $8\frac{1}{2}$  grains.

*September 6th.*—Fell asleep immediately after the injection, and slept eight hours. Has felt a great deal better; able to work, but weak.

*13th.*—Had a chill yesterday, and two to-day. Inject 5 grains.

*16th.*—Felt relieved in less than an hour after the injection, and has been well since.

*22d.*—Has had no recurrence.

**CASE V.**—McCue, aged eight years. Has been suffering almost incessantly, for some weeks, from intermittent, which has now assumed the quotidian type. He vomits so constantly now that he can take neither food nor medicine, and is much reduced. Inject  $4\frac{1}{2}$  grains. Felt better almost immediately, and in a few hours commenced eating, and retained his food.

**CASE VI.**—Mrs. C.

*June 3d.*—Irregular quotidian, with intense headache. Has had a variety of anti-periodic treatment, with little effect. Inject quinine, grs. vj.

28th.—Has had no paroxysm since last date, but has been on anti-periodics as a precaution. Is now under Dr. Murdock's charge for severe ophthalmia (iritis and corneitis), intense headache, and nausea. Has had hypodermics of atropine and morphine, but they make her "wild." Injected quinine, grs. vj.

29th.—Headache was promptly relieved, and she is much better to-day in every respect. The ophthalmia subsided rapidly.

**CASE VII.—Mrs. J. T.**

September 20th.—Sick for three days. Quotidian. Continual nausea, intense right supraorbital pain. Injected quinine, gr. vj. Pain was almost entirely relieved before the insertion of the second syringeful.

21st.—Better, and about the house. Slept well all night. No fever, no headache.

**CASE VIII.—Mrs. M. T.**

September 22d.—Tertian. In a violent paroxysm of fever now. Temperature 105°. Suffers especially from an intolerable "load or oppression" in epigastrium. Insists on an emetic. Injected quinine, grs. vj. Epigastric distress relieved before the first syringeful was completed, very much to the surprise and delight of both patient and doctor.

30th.—Quite well since.

**CASE IX.—M. K., aged sixty-two years.**

September 26th.—Feeble and asthmatic. Has been very ill for some time, with quotidian; the symptoms severe and almost continuous, reducing his strength very much. No sleep for several nights. Inject solution Magend., gr. xv, and to take quinine pills.

26th.—Slept well; but, as he could not retain the quinine, has had a severe chill to-day. Pulse frequent, and very feeble. Intense headache, semi-conscious. Inject quinine, grs. vj.

28th.—Went to sleep about an hour and a half after the injection, and slept well. Feels a great deal better, except the debility.

**CASE X.—Mrs. L. P.**

October 19th.—Suffering from quotidian for some days; the symptoms almost continuous. Has fever now, attended by violent "cramp" in the epigastrium. Inject grs. vj.

21st.—Says the cramp was relieved in fifteen minutes. Feels the pain returning in the stomach. Repeat injection, which again relieved the symptom in ten minutes.

24th.—No trouble since last date.

CASE XI.—Mary C., aged twenty-one.

November 1st.—Has had repeated attacks during summer. Has lately been taking twenty-seven grains of quinine daily, with no effect. Suffering now from most intense frontal headache. Inject grs. ix. Head-symptoms mitigated before the completion of the operation.

2d.—Slight cinchonism, but feels relieved of all painful symptoms.

CASE XII.—Anderson.

September 19th.—A feeble old man, suffering for some weeks from quotidian, and has been on quinine pretty regularly, with but little effect. Headache and nausea continuous; debility rather alarming. Injected quinine, grs. vj. Was almost immediately benefited.

20th.—Much better. Up and dressed, and eating, with a fair appetite.

Other cases, precisely similar to the above, might be quoted; but they are still very exceptional; and, in most of these cases, the disease recurred after a longer or shorter interval, and were again injected, or had other treatment.

Some cases of *malarious cephalic neuralgia* were promptly relieved, like the following:

CASE I.—A. H., aged fifty.

December 5th.—Had supraorbital neuralgia about four weeks since, and was relieved by an hypodermic injection of morph. et atropia, administered by Dr. Murdock. Since then, has had a regular paroxysm of febrile intermittent, and the neuralgia has recurred, and is periodical. Injected quinine, grs. viij.

December 31st.—Has had no return at all.

CASE II.—Mrs. T. B.

September 5th.—Has been troubled with malarious manifestations for eight months, previous to and after her confinement, these being confined mostly to cephalic pain and debility, never any regular paroxysm. They resisted all ordinary

anti-neuralgic remedies, and only yielded to large doses of quinine. Has been kept most of the time, since the attack was broken up, on quinine or chinoidine; for some time, has complained of a pain at the vertex, which has become severe and continuous, but worse at certain hours of the day. Six grains of quinine every night has kept it under somewhat, but does not remove it. Has also been on pills of iron, quinine, and strychnine, with no very good effect. To-day, injected quinine, gr. *vj.*

*September 9th.*—The headache has almost entirely subsided.

*January 9th.*—Has continued well, until about ten days since. Has now the same symptoms, but less severe. Inject 5 grains.

*February 1st.*—No pain since. Has taken no medicine since first injection.

In the following cases an unusual number of quinine injections were used, and *vomiting* occurred, also a most troublesome complication:<sup>1</sup>

**CASE I.**—Mrs. J. W., aged thirty-two. This patient has been more or less an invalid for a number of years, suffering from uterine disease, aggravated anteflexion, and endometritis. Four or five years ago, while pregnant, was attacked by low fever, of a remittent type, which could only be arrested for a time by quinine; finally, vomiting set in, and she was reduced to such a state of emaciation that the propriety of the induction of labor was discussed, but she pulled through. In

<sup>1</sup> Since this paper was written, I have received the January number of the *American Journal of Medical Science*, in which I find an article by Dr. George A. Musick, from which I quote the following: "For several days my patient's life 'hung by a thread,' the stomach rejecting every thing; but, by this method (hypodermic) it (quinine) was administered with facility, and its action was prompt. To it and the administration of sufficient nutriment by the rectum during the days of excessive gastric irritability, I believe my patient owes her life, more than to any thing else."

"I have given quinia by the *rectum*, both in *septicæmia* and in *pyæmia*, during my military service, but its absorption into the system was so slow that little if any good was accomplished by it. Had I given it at those times by hypodermic injection, I have no doubt that my success would have been greater."

1870, earlier in her pregnancy, she was threatened in the same manner, and Dr. Murdock, warned by former experience in her case, after consultation, brought on labor, and relieved her. Early in January, 1872, she again became pregnant, while suffering from malarious symptoms, and very soon uterine contractions, attended by pretty sharp pain, commenced ; and, as her stomach would retain no medicine, hypodermic injections of morphine were resorted to. She was under the charge of Dr. Murdock ; and we determined, in view of the chance of the anteflexion being corrected thereby, to carry her entirely through her allotted time, if possible. As the contractions commenced the moment she was entirely free from the influence of morphine, the anodyne injections were necessary to the end of the nine months, when a healthy child was delivered by the doctor, who proposes to give this interesting case in detail. Of these injections she had over three hundred during her pregnancy. At the same time, as it was impossible to give quinine by the mouth, and of the utmost importance that the malarious paroxysms should be prevented, it was found necessary to resort to the hypodermic injection of quinine ; and one containing six grains was given every six days throughout her pregnancy, except an accidental omission, which was followed by an attack, which prostrated her very much. She took, in all, forty of these injections, or eighty insertions. The insertions were all in the arms and thighs, and none of them were followed by the slightest local trouble.

CASE II.—Mrs. L. This is a still more interesting case, which has been under the charge of Dr. Murdock and myself for four or five years ; and, if it ever ends, Dr. M., who has had the *onus* of the case on his shoulders, purposes to give the details to the profession. Suffice it to say that, for the same reasons which influenced us in Case I., we were compelled to resort to hypodermics of morphine and quinine for several months, and are still going on with the latter ; and, as her uterine trouble, from which her other ailments have sprung, was a fibrous tumor, intramural, of considerable bulk, and not accessible to surgery, it was determined, after we had failed with other methods, to try ergot, and the hypodermic method was adopted ; so that, for the past year, or from De-

ember 28, 1872, to November 30, 1873, she has had 167 injections of Squibb's fluid extract of ergot, or over 6 ounces and a half. From July 21st to the present time, January 21, 1874, she has had an hypodermic dose of quinine, averaging 7 grains every six days; 29 injections, over 60 insertions, or 203 grains of quinine. For six months prior to September 1, 1872, she also required an hypodermic of morphine, combined always with atropine, our invariable custom now, daily; so that she has had, during a portion of the year, 182 injections of morphine and atropine, 167 of ergot, or 334 insertions of ergot, and 29 injections, or 60 insertions of quinine—a total of 576 syringefuls of the four drugs, and in only one instance after an injection of ergot, made by myself, did any considerable local trouble result, an abscess of the thigh—although the patient was in a most miserable condition of health all the time, kept alive for months on small portions of pulverized raw meat, champagne, brandy, and sometimes biscotine. A delay of a day or two in the quinine injection is sure to be followed by a severe paroxysm of intermittent, and now and then even within the six days. I will anticipate the further publication of the case by stating that the tumor has diminished at least two-thirds, and that the patient's condition now is better than it has been for a year, and she is steadily improving, all haemorrhages, which were extremely difficult to control, having ceased long since.

CASE III.—This patient, a feeble woman, aged about thirty years, was confined October 27, 1873, attended by Dr. Farrington, one of the resident physicians of Bellevue Hospital, who reported that she flooded both before and after confinement. The *post-partum* haemorrhage was promptly arrested, but she lost a sufficient quantity of blood to reduce her very greatly; and, as she had suffered for a long time from malaria, she subsequently became extremely anaemic. She was convalescing very slowly when mammary inflammation set in, abscesses formed, and simultaneously she was attacked by her old enemy malarious fever, and she was alarmingly reduced, the vomiting being extremely persistent. Neither medicine nor food could be retained on the stomach, nor could she bear enemata, on account of diarrhoea. Under the circumstances, Dr.

Murdock, who succeeded Dr. Farrington in the management of the case, resorted to hypodermic injections of quinine, which were commenced on December 6th, and continued either every day, or alternate days, until January 9, 1874, at which date she had had twenty injections, or forty insertions, averaging seven grains at each injection. The injections kept the disease at bay until December 25th, when she had a chill; since which date the nausea and vomiting, as well as the diarrhoea, having been promptly arrested by *electricity*, from six to twenty-four grains of quinine have been administered daily by the mouth in addition to that contained in the injections, as the case was so desperate that it was considered proper to saturate the system as freely as she could bear.

Notwithstanding this, so firm a hold did the malaria have on her system, that she had a return of the fever on December 30th, since which no manifestation has appeared, and she is improving daily. No local trouble has resulted from the injections, nor have they annoyed her enough to produce any complaint.

It has happened not unfrequently that a severe malarious attack immediately preceded, or coincided with, or succeeded parturition. In these cases the hypodermic injection had a particularly gratifying effect. I cite one case only in illustration of this class, as this paper has already become much more extended than was anticipated.

*Case reported by Dr. G. W. Murdock.*—Mrs. I. M., thirty-eight; confined by Dr. M., December 26th. Forceps at superior strait; every thing proceeded favorably till the 28th, just forty-eight hours after delivery, when she was attacked by a severe chill, attended by intense pain in head, back of neck, dorsal region, and abdomen; lochial discharge arrested; no mammary secretion; uterus enlarged and very tender; temperature,  $105^{\circ}$ ; pulse, 130. Injected quinine, grs. viij.; morph., gr.  $\frac{1}{2}$ , at 10 A. M. At 10 P. M., patient more comfortable. Temperature,  $103^{\circ}$ ; pulse, 100. Injected quinine, gr. iv.; morph., gr.  $\frac{1}{2}$ .

*December 29th.*—No fever; lochia re-established; milk appearing in breasts; temperature normal.

*30th.*—Doing well.



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